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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
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09/602,373 06/23/00 ZHU

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EXAMINER

FRASCHOFFER, T	
ART UNIT	PAPER NUMBER

1627
DATE MAILED:

03/20/01

Please find below and/or attached an Office communication concerning this application or proceeding.

Commissioner of Patents and Trademarks

Office Action Summary

Application No.

09/602,373

Applicant(s)

ZHU ET AL.

Examiner

Thomas W Prasthofer

Art Unit

1627

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 04 January 2001 and 19 January 2001.
- 2a) ☐ This action is FINAL. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-43 is/are pending in the application.
- 4a) Of the above claim(s) 25-43 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-24 is/are rejected.
- 7) ☒ Claim(s) 8 is/are objected to.
- 8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.
- 11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.
- 12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

- 13) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.
- 14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. & 119(e).

Attachment(s)

- 15) ☒ Notice of References Cited (PTO-892)
- 16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 17) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5.
- 18) ☐ Interview Summary (PTO-413) Paper No(s). _____.
- 19) ☐ Notice of Informal Patent Application (PTO-152)
- 20) ☐ Other: _____.

Detailed Action

Status of the Application

Receipt is acknowledged of an amendment and sequence listing on January 4, 2001 and January 19, 2001.

Status of the Claims

Claims 1-43 are pending in the present application. During a telephone conversation with Dr. Shirley Chen on March 13, 2001 a provisional election was made without traverse to prosecute the invention of Group I, claims 1-24. Affirmation of this election must be made by applicant in replying to this Office action. Claims 25-43 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention.

Election/Restriction

1. Restriction to one of the following inventions is required under 35 U.S.C. 121:
 - I. Claims 1-24, drawn to a method for generating a library of yeast expression vectors encoding fusion proteins using one or more homologous recombination steps, classified in class 435, subclass 471.
 - II. Claims 25-39, drawn to a method for generating a library of yeast expression vectors encoding fusion proteins using two or more homologous recombination steps, classified in class 435, subclass 463.
 - III. Claims 40-43, drawn to a method of producing a library of single chain antibodies in yeast, classified in class 435, subclass 69.6.

The inventions are distinct, each from the other because:

2. Inventions I and II are two different and patentably distinct methods for generating a library of yeast expression vectors because they use different starting materials and use different method steps. For example, the method of Invention I can be performed using only one homologous recombination step in which all of the fusion protein encoding DNA is introduced into the yeast expression vector. The method of Invention II requires a minimum of two homologous recombination steps and the DNA encoding the fusion protein is constructed in the yeast expression vector.
3. Inventions I and II and Invention III are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the methods of Inventions I and II produce expression vectors that can be used to produce a library of single chain antibodies by the method of Invention III. The method of Invention III can be practiced using yeast expression vectors that are made using restriction enzyme and ligation methods rather than homologous recombination. The methods of Inventions I and II can be used to produce libraries of fusion proteins that are not single chain antibodies.
4. Because these inventions are distinct for the reasons given above and
 - a. have acquired a separate status in the art as shown by their different classification ;
 - b. have different and separately burdensome: manual and/or computer: structure, name and bibliographical searches; and
 - c. have divergent subject matter, restriction for examination purposes as indicated is proper.
5. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

6. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a diligently filed petition under 37 CFR 1.48(b) and by the fee required under CFR 1.17(h).

Objections to the Claims

7. Claim 8 is objected to because it lacks a sequence identifier for the linker sequence [SEQ ID NO: 76].

Claims Rejections – 35 U.S.C. 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

8. Claims 1-24 are rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility.

The instant specification discloses that the claimed method is useful because it provides an “efficient and economical way to screen for fully human antibodies” and “the production and screening of the antibody libraries can be readily adopted for high throughput screening in vivo” e.g. see 28, lines 7-11. Page 29, lines 10-14 of the specification discloses “The highly complex primary antibody libraries can be used in a wide variety of applications. In particular, this library is used for screening of fully human antibody against a wide variety of targets, such as a defined antigen or a library of antigens associated with disease.”

Applicant's claimed method for generating a library of yeast expression vectors must satisfy 35 USC 101 and 112 (1) as defined by the statute and case law. In this regard, Applicant

is directed to MPEP 2107; 2107.01 and 210.02 which provide guidelines for determining the criteria for satisfying utility and enablement.

Initially it is noted that merely disclosing the ability to make a compound or compounds (e.g. a library) is in itself insufficient utility to satisfy either 35 USC 101 or 112, first paragraph as determined by the U.S. Supreme Court. . Eg. See *Brenner v. Manson*, 383 U.S. 519, 148 USPQ 689 (1966).

According to the text of 35 USC sec. 101, an invention must be "useful". Our reviewing courts have applied the labels, "specific utility" (or "practical utility") to refer to this aspect of the "useful invention" requirement of sec. 101. (*Nelson v. Bowler*, 626 F.2d 853, 206 USPQ 881, 883 (CCPA 1980)). In *Nelson*, the court characterized "specific utility" (or "practical utility") as "a shorthand way of attributing real-world value to claimed subject matter. In other words, one skilled in the art can use a claimed discovery in a manner which provides some immediate benefit to the public." (*Id.* at 856.)

With respect to the issue of pharmaceutical utility and vague assertions of biological activity applicant is further directed to *In re Kirk*, 376 F.2d 936, 941, 153 USPQ 48, 52 (CCPA 1967)) and *Cross v. Iizuka*, 753 F.2d 1040, 224 USPQ 739 (Fed. Cir. 1985), wherein the Federal Circuit labeled applicant's assertion of "biological activity" without more specifics as a "nebulous" expression. Such statements, the court held, "convey little explicit indication regarding the utility of a compound" and do not satisfy either the utility and/or the enablement statutory requirements.

The claimed method for generating a library of yeast expression vectors, is not supported by a specific asserted utility and does not, without further research and experimentation, provide an immediate benefit to the public.

Rather, the claimed method produces libraries of expression vectors that may encode any fusion protein that contains two subunits linked by a linker peptide. This includes all of the combinations of all protein subunits, known and unknown, of all species of organisms. This also includes purely synthetic sequences and sequences derived from mutagenesis. Given the universality of the fusion proteins that can be expressed from the claimed expression vectors, it is certain that some utility for the claimed method exists. The specific and/or substantial utility or utilities, however, are not disclosed as being known or possessed by Applicant. For example,

when the fusion proteins encoded by the expression vector are single chain antibodies, the method "produces libraries that can be "screened against virtually any protein or peptide target" (page 32, lines 23-24). This does not provide an immediate benefit to the public, however, because the disclosure does not provide any means or guidance for selecting protein or peptide targets or which targets have utility. Any benefit to the public (to one of ordinary skill in the art) is speculative.

Thus, the determination of utility is to take place at some future time, only when the properties of the selected test and/or target proteins have been elucidated. Absent a disclosure of those properties, the asserted utility lacks specificity. Note, because the claimed invention is not supported by a specific asserted utility for the reasons just set forth, credibility cannot be assessed.

This is not to say that inventions that are to be used exclusively in a research setting (i.e., research tools) always lack a specific asserted utility. Indeed, many research tools such as telescopes, gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility. (See USPTO Utility Guidelines, page 12.)

However, inventions that have a specifically identified utility must be distinguished from those whose utility requires further research to identify or reasonably confirm. (*Id.*) Research tools (such as gas chromatographs, screening assays, etc.) are useful in the sense that they can be used in conjunction with other method steps to evaluate materials other than themselves or to arrive at some result.

In the absence of an asserted specific utility, the "useful" requirement may be established by reference to a well established utility. A "well established utility" is a "specific utility" which is well known, immediately apparent and implied by the specification based on the disclosure of the properties of a material, alone or taken with the knowledge of one skilled in the art.

The method claimed is not supported by a well established utility, however, because neither the specification as filed nor any art of record discloses or suggests any property or activity for the expression vectors produced or molecules that they can be screened against such that another non-asserted utility would be well established for the claimed method.

Claims Rejections - 35 U.S.C. 112, 1st Paragraph

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

9. Claims 1-24 are also rejected under 35 U.S.C. 112, first paragraph. Specifically, since the claimed invention is not supported by either a specific and/or substantial asserted utility or a well established utility for the reasons set forth above, one skilled in the art clearly would not know how to use the claimed invention.

Claims Rejections - 35 U.S.C. 112, 2nd Paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

10. Claims 2-4 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "about" in the second line of each claim is a relative term which renders the claims indefinite. The term "about " is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The lengths of the 5' or 3' flanking sequences have been rendered indefinite.

11. Claim 16 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites that "the diversities of the first and second polypeptide subunits

are each independently derived from libraries of precursor sequences that are not specifically designed for a target peptide or protein.” Is the phrase intended to exclude fusion proteins in which either of the two subunits are known to bind to a particular peptide or protein that is not to be used as a target? Are fusion proteins composed of subunits known to or specifically designed to bind to small molecules excluded? Are naturally occurring proteins or subunits known to bind a particular peptide or protein considered to be “specifically designed” for a peptide or protein?

12. Claims 16 and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "derived from" is not defined by the claim or the specification. The term is used in claim 16 with respect to libraries of precursor sequences and in claim 17 with respect to proteins. There are no limits given as to the length of sequences that are considered to be “derived from” another sequence. A tripeptide sequence found in dozens of proteins may pose a problem because it can be “derived from” a protein or library specifically designed to bind or known to bind a target protein but the same tripeptide sequence could also be derived from a protein or library not known to bind a target protein.

13. Claim 17 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites that the diversities of polypeptide subunits “are not derived from one or more proteins that are known to bind to a target peptide or protein.” Does this mean that any polypeptide subunit derived from any protein that is known to bind to any target peptide or protein, specifically or non-specifically, is to be excluded from the library even if that target is not to be used in screening?

14. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim recites that the diversities of polypeptide subunits “are not generated by mutagenizing one or more proteins that are known to bind to a target peptide or protein.” Does this mean that any polypeptide subunit generated from a protein that is known to bind to any

target peptide or protein, specifically or non-specifically, is to be excluded from the library even if that target is not to be used in screening?

15. Claim 18 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "generated by mutagenizing one or more proteins" is vague and indefinite because the neither the claims nor the specification provide a definition of or a means of determining the degree to which polypeptide sequences can be mutated. Through mutagenesis (including, for example, deletion or insertions of 50% or more of a sequence) one might generate sequences that include sequence homology with proteins that were not among those used for the mutagenesis. There are no metes and bounds provided for one using the invention to determine the limitations of the term "generated by mutagenizing one or more proteins."

16. Claim 21 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "substantially conserved conformation" in claim 21 is a relative term which renders the claim indefinite. The term "substantially conserved conformation" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. The relative conformations between the first and second polypeptide subunits have been rendered indefinite.

17. Claim 22 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The term "mimics a conformation" in claim 22 is a relative term which renders the claim indefinite. The term "mimics" is not defined by the claim, the specification does not provide a standard for ascertaining the requisite degree, and one of ordinary skill in the art would not be reasonably apprised of the scope of the invention. In the context of the claim, "mimics" is used to indicate similarity in function or structure. One structure mimics another similar

structure to a degree but, without further qualification, the degree of structural similarity between molecules in order to say that one structure "mimics" the other is a matter of judgement and not definite.

Claims Rejections - 35 U.S.C. 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

18. Claims 1- 24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Hoeffler et al. (1999), WO 99/28502, Hua et al (1997) Plasmid 38:91-96, and Filupa et al. (1998) WO 98/49198.

The Hoeffler et al. reference teaches libraries of yeast expression vectors encoding libraries of single chain antibodies comprising a first nucleotide sequence encoding either V_H or V_L subunit, a second nucleotide sequence encoding either V_L or V_H subunit, and a peptide linker that connects the two subunits (see, for example, page 5, lines 1-16, page 7, lines 10-13, and figure 4). The yeast expression vectors include the yeast 2μ origin of replication (figure 4). The single chain antibody libraries are comprehensive populations of V_L and V_H subunits (vary independently from one another) linked by short, flexible peptide linkers (page 8, lines 16-17). The Hoeffler et al. reference presents an invention that can probe an animal's entire repertoire of > 10¹² combinations of light and heavy variable chains (page 11, lines 12-15, 21-22, and 25). The preferred linker in the Hoeffler et al. reference is a [(Gly)₄Ser]₃ peptide (page 24, line 27). The immunoglobulin variable regions can be amplified without prior knowledge of their sequences (or binding properties) (page 33, lines 5-6) and the fusions can be tagged with poly-Histidine for purification (page 43, lines 24-25).

The Hoeffler et al. reference does not explicitly teach the use of linker sequences between 45-102 or 45-63 bp in length or the use of homologous recombination to clone expression libraries in yeast.

The Filupa et al. reference teaches the synthesis of single chain antibody expression vectors in yeast and states that the preferred peptide linker should be from 2 to about 50 or 18 to about 30 residues (page 21, lines 23-24 and page 22, lines 17-18).

The Hua et al. reference teaches homologous recombination as a cloning technique as well as flanking homologous sequences of 30-38 and 20-60 bp in length (page 91, column 2 and page 92, column 2, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time that invention was made to produce the expression vectors of Hoeffler et al. using the methods of Hua et al. One would have been motivated to do this because homologous recombination cloning techniques can produce libraries with higher diversity than more conventional cloning techniques. One would have had reasonable expectation of success because recombination techniques had already been used to generate highly diverse single chain antibodies in phage and bacteria and the use of recombination techniques in yeast were well known at the time that the invention was made.

19. Claims 1-24 are rejected under 35 U.S.C. 103(a) as being unpatentable over Filupa et al. (1998) WO 98/49198, Hua et al (1997) Plasmid 38:91-96, and Hoeffler et al. (1999), WO 99/28502.

The Filupa et al. reference teaches a number of different single chain antibody (SCA) fusion protein yeast expression vectors and yeast transformed with these vectors. The vectors comprise nucleotides encoding V_L and V_H subunits connected by linker sequences (page 2, lines 9-12, page 8, lines 6-11, and page 9, lines 12-20). The V_L and V_H subunits may encoded in either order from 5' to 3' (page 19, lines 9-27). The preferred peptide linker should be from 2 to about 50 or 18 to about 30 residues (page 21, lines 23-24 and page 22, lines 17-18). At east 18 different expression vectors are taught that comprise sequences in the two subunits that vary independently of one another (page 29, line13 – page 30, line 22, page 67, lines 15-17, and page 76, claim 1.). The reference teaches that other proteins may also be modified including cell

adhesion proteins, IgA, IgG, IgD, IgE, IgM, enzymes, cytokines, and growth factors (page 30, line 26 - page 31, line 14). The yeast expression vector includes the yeast 2 μ circle (page 35, line 4) and is transformed into yeast (page 36, lines 8-10).

The Filupa et al. reference does not explicitly teach a repeated GGGGS linker sequence, libraries with diversities of greater than 10³, affinity tags, or homologous recombination.

The Hua et al. reference teaches homologous recombination as a cloning technique as well as flanking homologous sequences of 30-38 and 20-60 bp in length (page 91, column 2 and page 92, column 2, first paragraph).

The Hoeffler et al. reference presents an invention that can probe an animal's entire repertoire of > 10¹² combinations of light and heavy variable chains (page 11, lines 12-15, 21-22, and 25). The preferred linker in the Hoeffler et al. reference is a [(Gly)₄Ser]₃ peptide (page 24, line 27). The immunoglobulin variable regions can be amplified without prior knowledge of their sequences (or binding properties) (page 33, lines 5-6) and the fusions can be tagged with poly-Histidine for purification (page 43, lines 24-25).

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to make the single chain antibodies of Filupa et al. using the method of Hua et al. and to generate libraries of single chain antibodies for screening as in Hoeffler et al. One would have been motivated to do so because recombination methods can produce single chain libraries of greater diversity than more conventional cloning methods and recombination methods avoid several time consuming cloning steps. The motivation for making libraries would have been to screen for antibodies that bind to specific antigens of interest. One would have had reasonable expectation for success because both recombination methods of cloning in yeast and expression of single chain antibodies in yeast were known in the art.

20. Claims 1-4 and 10-19 are rejected under 35 U.S.C. 103(a) as being unpatentable over Griffiths et al. (1999) U.S. Patent No. 5,962,255 and Hua et al (1997) Plasmid 38:91-96.

The Griffiths et al. reference teaches a recombination method for the production of bacterial expression vectors comprising two-subunit fusion proteins including fusion proteins that are single chain antibodies in which the subunits are joined by linkers (column 10, lines 26-

46 and column 11 lines 57-65). The Griffiths et al. reference also teaches bacterial expression vectors with library diversities greater than 10^{12} .

Griffiths et al. do not explicitly teach the production of expression vectors in yeast or specific lengths for flanking sequences used in homologous recombination.

The Hua et al. reference teaches homologous recombination as a cloning technique in yeast cells as well as flanking homologous sequences of 30-38 and 20-60 bp in length (page 91, column 2 and page 92, column 2, first paragraph).

It would have been obvious to one of ordinary skill in the art at the time that the invention was made to combine the method of Griffiths et al. with those of Hua et al. to generate the single chain antibodies of Griffith et al in yeast. One would have been motivated to do so because yeast cells, unlike bacteria, can glycosylate the antibodies as humans and other eukaryotes do, thus producing antibodies with biological properties more similar to human antibodies. One would have had reasonable expectation for success because homologous recombination techniques in yeast as well as antibody production in yeast were known in the art at the time that the invention was made.

21. Any inquiry concerning this communication or earlier communications from the examiner should be directed to **Thomas W. Prasthofer** whose telephone number is **(703) 308-4548**. The examiner can normally be reached on Monday-Friday, 8:00-4:30.

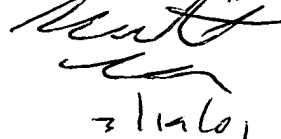
22. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jyothsna Venkat can be reached on (703) 308-2439. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-2742.

23. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-1235.

Thomas Prasthofer, Ph.D.

3/17/01

BENNETT CELSA
PRIMARY EXAMINER



3/14/01